UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,004	02/12/2001	Bassil I. Dahiyat	067461-5041-US01	1900

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EXAMINER
BORIN, MICHAEL L

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.
- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _23 October 2007_.
2a)☐ This action is **FINAL**.   2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _36-41_ is/are pending in the application.
   4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) _36-41_ is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
   Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
   Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All   b)☐ Some * c)☐ None of:
      1.☐ Certified copies of the priority documents have been received.
      2.☐ Certified copies of the priority documents have been received in Application No. _____.
      3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
   * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO/SB/08)
   Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413)
   Paper No(s)/Mail Date. _____.
5)☐ Notice of Informal Patent Application
6)☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set

forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this

application is eligible for continued examination under 37 CFR 1.114, and the fee set

forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action

has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on

10/23/2007 has been entered.

Rejections not reiterated from previous Office actions are hereby withdrawn.

Amendments to claim 1 obviated the rejections of record and necessitated new ground

of rejection. The following rejections constitute the complete set presently being applied

to the instant application.

Status of Claims

1.   Claims 36-41 are pending. Claim 36 is amended.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly
> claiming the subject matter which the applicant regards as his invention.

2.   Claims 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. In claim 36, it is not clear how applying force field

calculation to particular <u>residue</u>, per step c) will result in a <u>library</u>, rather than a set of energy-optimized residues. It seems that a step of recombining the optimized residues into sequences is omitted.

Further, it is not clear in which way primary library is different from secondary libraries. In the case that native residue is energy-optimal, which is often the case, the "optimized" sequences in primary library will comprise the native residues - i.e., the "set" addressed in step d) will comprise both "variant" residues and "native" residues – and thus the secondary library will be the same as primary. Is secondary library obtained by random permutation of energy-optimal and "less-optimal" residues from the set?

Claim Rejections - 35 USC § 102 and 103

3.   Claims 36-41 are rejected as being unpatentable over Wang et al (Protein Engineering, 9 (6), 479-484, 1996) and Dahiyat,1997 (J. Mol. Biol., 1997, 273, 789-796).

The claims are directed to method for generating of at least one non-naturally occurring variant protein with at least one desired characteristic relative to a target protein comprising:

a)   inputting the coordinates of said target protein into a computer;

b)   identifying a list of variable residue positions in said target protein based upon said at least one desired characteristic

c)   applying a force field calculation to said variable residue positions to generate a primary library comprising optimized variant protein sequences;

d)   generating a set of amino acid residues at each of said variable residue positions

by combining:

- (i) at least one variant amino acid in said primary library at said variable residue

  position, and

- (ii) the amino acid residue of said target protein at said variable residue position;

e)   generating a plurality of protein sequences by combining into the sequence of

said target protein each of said set of amino acid residues at each of said variable

residue positions to generate a secondary library of protein sequences, wherein at least

one member of said secondary library is not found in said primary library; and

f)   synthesizing a plurality of said secondary library protein sequences and

screening said sequences to identify at least one non-naturally occurring variant protein

with said at least one desired characteristic.

Wang et al teach use of force field to design protein variants. Based on protein

main chain characteristics, the mean force field was constructed to evaluate the

compatibility between an amino acid residue and its environment, from which a position-

dependent protein mutant profile was constructed. At each position along a protein

sequence, the native residue was replaced by the other 19 types of amino acid

residues. The reference concludes that creating such libraries can be used as a guide in

protein engineering and as an effective scoring matrix in protein sequence–structure

alignment studies.

In particular the method comprises the following steps which are correlated to

the steps of the instant method as follows:

Instant claim 36	Wang et al
a) inputting the coordinates of said target protein into a computer;	See p. 479, bottom.
b) identifying a list of variable residue positions in said target protein based upon said at least one desired characteristic	In Wang's case, all residues are "variable". see obviousness part of rejection below.
c) applying a force field calculation to said variable residue positions to generate a primary library comprising optimized variant protein sequences;	For each residue in the sequence, Wang applies force field calculation to 19 other natural amino acid residues. This is viewed as generating a "primary library"

| d)   generating a set of amino acid residues at each of said variable residue positions by combining:

• (i) at least one variant amino acid in said primary library at said variable residue position, and

• (ii) the amino acid residue of said target protein at said variable residue position, and

e)   generating a plurality of protein sequences by combining into the sequence of said target protein each of said set of amino acid residues at each of said variable residue positions to generate a secondary library of protein sequences, wherein at least one member of said secondary library is not found in said primary library | Fig 1 in Wang compiles sequences obtained by generating sets of residues for each "variable residue" in the order of energy efficiency and recombining them into sequences in the order of sequence of the original protein. Since for each position Fig. 1 comprises both the substituted residues (i.e., residues from "primary library") and the native residue, it results in a set as per step d), and a library as per step e). Since the latter library is comprised of sequences comprises native residues in addition to mutant residues in "primary" library, it is different in at least one member from the library comprised only of mutant residues. |

Wang does not teach identifying particular residues based upon said at least one desired characteristic. However, it would be obvious to one skilled in the protein

modeling art that mutation of all residues of target protein would be exhaustive and

useless and it will completely obliterate the functions of the original protein. Usually

performed is such modifying of residues that seem to be beneficial. see, for example

Dahiyat, 1997. When there is motivation to solve a problem and there are a finite

number of identified, predictable solutions, a person of ordinary skill has good reason to

pursue the known options within his or her technical grasp. If this leads to anticipated

success, it is likely the product not of innovation but of ordinary skill and common sense.

Thus, Examiner consider obvious first identifying particular residues of interest in the

method of Wang et al.

Further, Wang et al does not explicitly teach synthesizing a plurality of protein

sequences and screening their activity. However, it would be obvious to one skilled in

the art that the desirable end stage of any protein modeling is synthesis of proteins of

interest and verifying its desirable functions.

Further, with regard to claims 37-41, selection of PCR method to synthesize

proteins would be obvious to an artisan as it is one of the main methods of protein

synthesis, and selection of particular parameters of PCR would be obvious to an artisan

as a part of routine selection of optimal parameters.

Conclusion.

6.   No claims are allowed

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Michael Borin whose telephone number is (571) 272-

0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number

for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information

system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Borin, Ph.D.
Primary Examiner
Art Unit 1631

mlb